Discovery of the sulphonylureas

Professor Robert Tattersall

Today's diabetes world is fast moving and exciting; knowledge is accumulating at an astonishing rate. To help understand the present, however, it sometimes helps to examine the past.

In this installment of *Tattersall's Tales*, Robert Tattersall describes the discovery of the sulphonamides, their use in various infectious diseases and urinary tract infections to their use in diabetes and the early issues with the use of these drugs.

The hypoglycaemic sulphonylureas were a serendipitous offshoot of the search for antibacterial agents in the 1930s and 40s. At a time when people could die of septicaemia from a simple cut, curing infection was more important than research into diabetes – where diet and insulin were regarded by doctors, if not patients, as adequate treatments. In 1932, Gerhard Domagk (1895–1964), Director of Reseach at Bayer AG, Germany, did an experiment with the red dye, 'Prontosil', in which two groups of 12 and 14 mice were infected with streptococci. Those treated with the dye survived at least a week, but all the untreated mice died in four days – no need for statistics here! In 1935, it was shown that a simpler compound, sulphanilamide (a breakdown product of Prontosil and a chemical which had been synthesised as early as 1908) was equally effective against erysipelas, puerperal fever and scarlet fever. Between 1939 and 1942 use of sulphonamides increased dramatically, and they were tried in the treatment of most infectious diseases (Weatherall, 1990).

In spring 1942, Marcel Janbon of the Montpellier Medical School used a new sulphonamide – 2254RP – synthesised by the French Rhône-Poulenc Society to treat 30 patients with typhoid. Several of the rather emaciated patients died and others had fits or lapsed into coma. Many, if not all, became hypoglycaemic. The drug was further investigated by the physiologist August Loubatières (1912–1977) who found that an oral dose in fasting dogs caused progressive and severe hypoglycaemia. The glucose-lowering effect was seen in partially depancreatised animals but not after total pancreatectomy. The degree of hypoglycaemia depended on the plasma concentration of the drug, but even low doses caused a marked fall in blood glucose levels when injected directly into the pancreatic artery. These observations led Loubatières to suggest that the drug stimulated insulin release from the pancreas. Since it still worked if only a tenth of the pancreas was left, he thought that 'It might be effective in diabetes, provided a certain quantity of functionally healthy islet cells remained in the pancreas' (Loubatières, 1957). This work, published mainly in French, went largely unnoticed and it is not known why the makers of the drug failed to follow it up.

The story of carbutamide, the first sulphonylurea to be marketed, is murky and unedifying. It was originally synthesised in 1945 by Ernst Carstens, a chemist in the laboratory of the Chemische Fabrik Von Heyden in Dresden. It was marketed in, the by then communist, East Germany in 1950 for the treatment of urinary tract infections. Initial clinical trials by Hellmuth Kleinsorge (born 1920) showed a high frequency of hypoglycaemic symptoms. In 1952, Kleinsorge presented his findings to the company and the Head of Research Erich Haack (1904–1968). In 1953 the East German Ministry of Health banned the drug and forbade further research on it, which prevented Kleinsorge from publishing his work. That same year, Haack moved to West Germany where he joined Boehringer Mannheim which synthesised and patented the drug and arranged for it to be tested at the Auguste Victoria Hospital in West Berlin. Haack promoted the drug as an antibacterial and did not mention the side effect of hypoglycaemia (Kleinsorge, 1998). The young doctor who did the tests, Karl Joachim Fuchs, noticed that the drug produced psychomotor excitement, speech disturbances and temporary apathy. To find the cause of these symptoms, Fuchs himself took it and developed ravenous hunger and euphoria. His symptoms were abolished by eating lunch and were found to be due to hypoglycaemia. Studies in around 200 patients with diabetes followed and were published in three reports in the *Deutsche Medizinische Wochenschrift* in 1955. The general conclusion was that carbutamide was most effective in people over 45 years of age who had had diabetes for less than 5–10 years and not used insulin for more than 1–2 years.

These reports aroused great interest among people with diabetes and their doctors, and in June and August 1956 whole issues of the *Canadian Medical Association Journal* and the *British Medical Journal* (BMJ) were devoted to studies of carbutamide, respectively. The *BMJ* took a holier-than-thou approach claiming that diet was ignored in most of the German patients so that far more were on insulin than would have been the case in a British clinic where 'they would be dieted without insulin'. Hence, according to the *BMJ*, 'even if the German claims were sustained, [carbutamide] would be indicated only in comparatively few cases' (Editorial, 1956).

One reason for the reservations of the anonymous editorialist was uncertainty about how carbutamide worked. The usual revisionist medical histories would have one believe that, even had they been widely known (which they were not), it was obvious from Loubatières' experiments that they worked by stimulating insulin secretion. This theory was actually received with considerable scepticism, especially when histological studies in the early 1950s suggested damage to the alpha cells which were strongly suspected of producing glucagon. Interestingly, in his 1956 article in the *BMJ*, the influential biochemist Frank Young wrote (Young, 1956):

> *'When one considers the range of substances which exert some degree of hypoglycaemic and antidiabetic action – guanidine derivatives, acridines, sulphonamides and penicillin – one is struck by the fact that all possess some anti-microbial action. Can these two actions be reasonably related?'*

The theoretical basis for relating them came from studies which suggested that the livers of many animals normally contained a range of bacteria, and Young wondered if their normal function was to break down insulin. The increased insulin need during severe infections seemed to him to support this theory.

Writing in *Diabetes* in January 1956, Arthur Colwell (1897–1978) suggested that the favoured hypothesis was that carbutamide

suppressed glucagon secretion because histology of the pancreas of animals treated with it had shown damage to alpha cells. Other possibilities, according to Colwell, included 'accelerated release of insulin from the pancreas, suppression of insulinase, other hepatic effects and suppression of pituitary or adrenal function' (Colwell, 1956). He ended with a warning:

'Those who witnessed the transient enthusiasm regarding the guanidine compound Synthalin (which also originated and was marketed in Germany until lenticular, hepatic and renal damage were encountered after sustained use) will welcome long, well-controlled studies by earnest and experienced investigators. To yield to the pressure of healthy diabetics for an easier way than insulin might do more harm than good.'

Another reason for the cautious attitude to the new drugs was concern that, in the words of the *BMJ*, prolonged use would lead to 'undesirable metabolic or somatic consequences' (Anonymous, 1956). Sulfanilamide had been introduced in the US in 1936 and was intitially hailed as a miracle drug especially after it was given to Franklin Roosevelt Jr. However, within a few years it became clear that sulphonamides could cause fatal toxic reactions and blood dyscrasias (Dowling, 1977). Dangerous side effects had to be accepted in critically ill patients with infections, but, as the BMJ noted, diet was already a safe and physiological remedy for type 2 diabetes and any proposed alternative must be equally innocuous. Among the 193 English patients on whom carbutamide was tested in 1956, a rash had developed in 9% and a few had neutropaenia or fatal agranulocytosis. In the US it was withdrawn by Eli Lilly and Company, and the problem of its toxicity was neatly summed up by their research director Franklin Peck (Peck, 1957):

'Actually the toxicity of carbutamide is comparatively quite low. Certainly it would be no deterrent to treatment of any serious temporary illness, eg., pneumonia, nor would it be considered serious if no other safe treatment were available for diabetes. It is a nice question to contemplate – how much toxicity can be tolerated in a drug used in the management of a disease which may extend over an ordinary lifetime?'

Introduction of the sulphonylureas led to some disasters with individual patients. In Edinburgh, it was the practice of Leslie Duncan and Joyce Baird to stop insulin abruptly and see the patient 3 or 4 days later. They discontinued this after one woman who had been 'sugar free' for several years on only 16 units of insulin a day was admitted to hospital in deep coma only three days after stopping insulin. They also noted that in Germany the incidence of diabetic coma 'increased alarmingly' in the few months after the release of carbutamide for general prescription (Duncan and Baird, 1957).

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